A multicenter validation of an endoscopic classification with narrow band imaging for gastric precancerous and cancerous lesions

Authors P. Pimentel-Nunes[1,2,*], M. Dinis-Ribeiro[1,3,*], J. B. Soares[2,4], R. Marcos-Pinto[5], C. Santos[3], C. Rolanda[4,6], R. P. Bastos[7], M. Areia[8], L. Afonso[9], J. Bergman[10], P. Sharma[11], T. Gotoda[12], R. Henrique[9,13], L. Moreira-Dias[1]

Institutions Institutions are listed at the end of article.

submitted 4. March 2011
accepted after revision 14. October 2011

Bibliography
DOI http://dx.doi.org/10.1055/s-0031-1291537
Published online: 31.1.2012
Endoscopy 2012; 44: 236–246

ISSN 0013-726X

Corresponding author
M. Dinis-Ribeiro, MD
Department of Gastroenterology
Portuguese Oncology Institute of Porto
Rua Dr. Bernardino de Almeida
4200-072 Porto
Portugal
Fax: +351-22-5084055
mario@med.up.pt

Background and study aim: The reliability and external validity of narrow band imaging (NBI) in the stomach have not been described consistently. The aim of the current study was to describe and estimate the accuracy and reliability of a simplified classification system for NBI in the diagnosis of gastric lesions.

Methods: Consecutive patients undergoing NBI endoscopy at two reference centers (n = 85, 33 % with dysplasia) were included in two studies. In total, 224 different areas were biopsied and recorded onto video. In the derivation study, previously described NBI features were analyzed in order to develop a simplified classification. In the validation study the accuracy and reliability of this classification were estimated among three groups of endoscopists with different levels of expertise in NBI.

Results: The reliability/accuracy results from the derivation study allowed the creation of a simplified NBI classification. In the validation study, "regular vessels with circular mucosa" (pattern A) was associated with normal histology (accuracy 83 %; 95 % confidence interval [CI] 75 % – 90 %); "tubulo-villous mucosa" (pattern B) was associated with intestinal metaplasia (accuracy 84 %; 95CI 77 % – 91 %; positive likelihood ratio [LR +] = 4.75); and "irregular vessels and mucosa" (pattern C) was associated with dysplasia (accuracy 95 %; 95CI 90 % – 99 %; LR + = 44.33). The reproducibility of these patterns was high (k = 0.62). "Light-blue crest" was moderately reliable (k = 0.49) but specific (87 %) for intestinal metaplasia. A variable vascular density (additional pattern +) was the best feature for *Helicobacter pylori* gastritis (accuracy 70 %; 95CI 59 % – 80 %) but showed only fair reliability (k = 0.38). Non-experienced endoscopists presented lower agreement (k = 0.6 vs. k = 0.75) and accuracy (74 % vs. 86 %) than international experts/experienced endoscopists.

Conclusion: A simplified NBI classification is accurate and reliable for the diagnosis of intestinal metaplasia and dysplasia. The classification should be further assessed and validated on a per-patient assessment of NBI, and by comparing NBI with other imaging technologies.

Introduction

Gastric adenocarcinoma is the second most lethal cancer worldwide with only a minority of gastric adenocarcinomas diagnosed in a curable and resectable form [1,2]. *Helicobacter pylori* is considered the most important risk factor for gastric cancer, by promoting a multi-step process of chronic gastritis, atrophy, intestinal metaplasia, dysplasia and, finally, intestinal-type adenocarcinoma [3]. Secondary prevention through diagnosis of premalignant lesions and early gastric cancer, and screening or follow-up of individuals at high risk, would probably be the most immediate strategies for improving survival [4, 5]. Endoscopy examination is therefore of paramount importance. However, endoscopic evaluation of gastric mucosa correlates poorly with histological findings [6,7], and it is not surprising that ancillary techniques such as chromoendoscopy have been used for an accurate diagnosis of precancerous lesions and/or invasiveness of cancerous lesions [8 – 10]. Even so, for diverse reasons these methods are not very popular among endoscopists, particularly those in Western countries.

Diverse descriptions of new methods of electronic chromoendoscopy, namely high resolution with narrow band imaging (NBI), with or without magnification, have been published [11 – 24]. Good results have been reported for the imaging of intestinal metaplasia and cancer; however, reliability

* The authors contributed equally to this study and should be considered joint first authors.

has seldom been evaluated, no study has included the whole spectrum of lesions, and no external validation of any defined features has been reported [25].

Thus, the aims of the current study were: to assess the reliability of previously described NBI features for gastric precancerous and neoplastic lesions; to simplify the features under a new classification; and to validate this classification on a new sample of patients and observers, and to assess the accuracy of the classification system in endoscopists with a range of NBI experience.

Methods

Study design and selection of patients

Patients undergoing routine upper gastrointestinal endoscopy at two hospitals in the North of Portugal (Portuguese Oncology Institute of Porto and Braga's Hospital), between September and December 2009 and between February and April 2010, were consecutively considered and included in this study after giving informed consent. Both hospitals are tertiary centers to which patients with superficial lesions are referred and treated with minimally invasive techniques [26]. Patients with chronic liver disease, psychiatric conditions, anticoagulant therapy or coagulation disorders, were excluded. The ethical committees of both hospitals approved the study.

Two studies were planned (see **Fig. e1**, available online only):

- the first 45 patients (estimated sample of 100 videos), who were treated between September and December 2009, constituted the "derivation cohort," which provided data for a study on the reliability of previously described mucosal and vascular features of gastric mucosa using NBI [11–24]. These data were used to derive a simple NBI classification and were also subject to validity testing using histology as the reference test;
- in the second study, a "validation cohort" of 40 new patients (and a new estimated sample of 100 videos), who were assessed between February and April 2010 using endoscopic observations, provided data for the validation of the new NBI classification and assessment of the reliability of the classification within groups of endoscopists with diverse experience.

Endoscopic procedures and selection of videos

Under pharyngeal anesthesia (85% of the patients) or deep sedation (15% of patients) all patients underwent upper gastrointestinal endoscopy using a high resolution (HR) Olympus endoscope with NBI (EVIS EXERA II video system center GIF-180; Olympus, Tokyo, Japan). Detailed observation of esophageal, gastric, and duodenal mucosa was performed and all endoscopic lesions were described accordingly. High resolution videos of low magnification (×1.5) NBI endoscopy were recorded for further analysis from (subject to patient tolerance) five areas of antral, incisura, and corpus mucosa. Recordings were also made from those areas with endoscopic changes, either at high resolution white light endoscopy (HR-WLE) or at HR-NBI. A shift between the HR-WLE and HR-NBI was used to ensure the position and precision of the biopsies taken. The total number of histological samples was equal to the total number of videos recorded. From all of the procedures, 140 (derivation study) and 119 (validation study) videos of approximately 10 seconds in duration were recorded consecutively and converted into MPEG-4 files of approximately 10 MB each using iMovie (Apple Inc., Cupertino, California, USA). No area was recorded twice. Each video was labeled with a random number and transferred onto a computerized database. Of the 259 videos recorded only those showing highest quality images of mucosal morphology and in which the video observation confirmed the targeting of the biopsies were selected for use in the respective studies(124 in the derivation study and 100 in the validation study). The quality of the videos was assessed by one experienced endoscopist. The whole potential spectrum of histological lesions (no intestinal metaplasia or dysplasia [normal mucosa], presence of intestinal metaplasia, presence of dysplasia [or carcinoma], and presence of *H. pylori* irrespective of histology, excluding dysplasia) was considered for video selection, both for the derivation study and for the validation study.

Histopathological procedures

All gastric mucosa specimens were obtained by endoscopic biopsy at each area selected for video recording, with the exception of videos recorded from superficial lesions where a whole mucosectomy specimen was obtained. Specimens were fixed in buffered formalin, processed for paraffin embedding, sectioned, and stained with hematoxylin and eosin. Gastric specimens were also evaluated for *H. pylori* infection using modified Giemsa (2%) stain. Two expert gastrointestinal pathologists, who were blind to the NBI features, made the final histological diagnosis according to the Sydney–Vienna classification [27,28].

Selection of endoscopists

For the derivation study (reliability assessment of previously described NBI features), three endoscopists (End1, End2, and End3) who had previous clinical experience of NBI (>50NBI gastroscopies) each assessed all of the videos; they were blinded to histology and to the evaluation of the other endoscopists. Endoscopists were instructed to evaluate the videos using previously reported mucosal and vascular features when these features were applicable to NBI with low magnification [11–24]. In order to overcome the problem of an irregular pattern being assigned different meanings and being associated with different pathologies such as *H. pylori* infection [11], intestinal metaplasia [12], and dysplasia/cancer [16,18], the endoscopists were instructed to state the pattern as "irregular" only when they observed a complete architectural loss of the mucosal or vascular pattern (see below for definition of variables).

In the validation study, nine observers were included:

- the three experienced endoscopist observers (End1, End2, and End3) who participated in the derivation study;
- three different gastroenterologists who had not participated in the first assessment, and who had special interest in chromoendoscopy but with diverse NBI experience (<50NBI gastroscopies); these were designated non-experienced observers;
- and three international expert NBI endoscopists (from Europe, USA and Japan); these were designated the expert observers.

All of the observers classified the second set of videos after receiving a pen drive with a PowerPoint presentation (Microsoft Office 2003, Microsoft Inc., Redmond, Washington, USA), which contained the rationale of the derived classification and example videos.

Variables

In the derivation study the following variables were included [11–24].

- Mucosal pattern: regular circular (well delineated circular/oval glands), regular tubulo-villous (well delineated tubulo or villous or ridge glandular pattern) or irregular (glandular pattern

is clearly irregular with architecture distortion with absent glandular pattern in some areas possible).

- Light blue crest (LBC): presence (yes) or not (no) of blue-whitish slightly raised areas.
- White opaque substance (WOS): presence (yes) or not (no) of white material above the mucosa that could be either well defined (regular) or not (irregular).
- Vascular pattern: regular (vessels well defined in the center or surrounding the glands) or irregular (areas with clearly anomalous vessels associated with architecture distortion of the mucosa). If there were areas where vessels were not seen clearly but without anomalous configurations they were included in the regular group.
- Vascular thickness: subjective opinion of normal/thick vessels or somewhat thin or ultrathin.
- Vascular density: high density (almost all of the glands are surrounded by reddish vessels with some areas with vessel agglomerates possible) or low density (vessels are not seen clearly surrounding all of the glands, pale colored vessels).
- Variable vascular density (VVD): presence (yes) or not (no) of alternating areas of high and low density in the same video.

To assess the reliability of these features for inclusion in the classification, each video was classified by all observers according to these NBI features and a grade for certainty was assigned. In addition, each observer was asked to make an histological diagnosis based on the NBI features and, again, to assign this diagnosis a grade of certainty. Histopathological assessment was considered to be the gold standard or reference test for accuracy estimates.

Statistical analysis

The Statistical Package for Social Sciences (SPSS 17.0 Package Facility, SPSS Inc., Chicago, Illinois, USA) was used for data support and analysis.

The proportion of overall agreement was the proportion of cases for which two observers agreed. The proportions of specific agreement relative to each category was an estimation of the probability of, given that one observer makes a rating in a category, that the other observers will rate the same. The generalized formulae, for more than two observers, for the proportions of overall and specific agreement, were calculated by dividing the total number of actual agreements by the total number of possible agreements. Light's Kappa (mean of the kappa values obtained from each pair of raters) was also calculated. The nonparametric bootstrap was used to estimate the 95% confidence intervals (CIs). Strength of agreement was considered as follows: slight 0 – 0.2; fair 0.2 – 0.4; moderate 0.4 – 0.6; substantial 0.6 – 0.8; almost perfect 0.8 – 1.

For estimation of sample size, a target estimate standard error of 0.1 in kappa values was determined. Each video classification was compared with the histological diagnosis of the corresponding specimens (gold standard or reference test). Sensitivity, specificity, and global accuracy were estimated separately and for all nine observers combined, along with the 95%CIs. Likelihood ratios (LR) were estimated based on mean sensitivity and specificity estimates.

Results

Derivation study

Description of participants and videos

Patient characteristics and a description of endoscopic procedures included in the study are shown in **Table 1**. In 20% of the patients five or more biopsies were possible and in 28% four biopsies of different areas were performed. Due to the specialist nature of the institutions, a large number of endoscopic examinations were performed for dysplasia or mucosectomy (36%). This yielded a significant number of histological samples of dysplasia (n = 23) and metaplasia (n = 40). A total of 124 good quality videos (67 normal mucosa, 34 intestinal metaplasia, and 23 dysplasia

Table 1 Description of participants and endoscopic procedures (n = 85).

Patients	Total n = 85	Derivation n = 45	Validation n = 40
Male sex, n (%)	50 (59)	28 (62)	22 (55)
Age, mean (range), years	61 (21 – 91)	61 (21 – 91)	61 (49 – 80)
Number of biopsies, median (range)	3 (1 – 6)	3 (1 – 5)	3 (1 – 6)
Indications for upper gastrointestinal endoscopy, n			
Follow-up/previous diagnosis of dysplasia	23	11	12
Dyspepsia	16	12	4
Follow-up after precursors conditions (metaplasia)	16	6	10
Follow-up after gastric mucosectomy	14	8	6
For gastric mucosectomy	11	5	6
Other (e. g. GERD)	5	3	2
Main endoscopic findings, n			
Gastric superficial lesions	21	11	10
Normal	17	13	4
Papular-erythematous gastritis	15	8	7
Gastric scar	13	6	7
Gastric irregularity	11	5	6
Erosive gastritis	8	2	6
Histological diagnosis per patient, n			
Normal mucosa (antrum and body)	21	12	9
Intestinal metaplasia antrum	22	11	11
Intestinal metaplasia corpus	14	8	6
Dysplasia (one or more areas)	28	14	14
H. pylori infection	38	21	17

GERD, gastroesophageal reflux disease.

Table 2 Derivation study: correlation between features of narrow band imaging and histology; according to observer classification (End1, End2, and End3) reliability measures are estimated (proportion of agreement and specific proportions of agreement [Pa] and kappa [k]) for previously described features (n = 124).

	Histological findings, %				Observer classification[1], n (%)			Reliability [95 %CI]	
	Normal	Intestinal metaplasia	Dysplasia	H. pylori	End1	End2	End3	Pa	K
Mucosal pattern								0.82 [0.77 – 0.87]	0.71 [0.62 – 0.80]
Regular, circular	86	9	1	51	56 (45)	64 (52)	62 (50)	0.84 [0.78 – 0.89]	
Regular, tubulo-villous	12	89	3	45	39 (32)	36 (29)	39 (32)	0.73 [0.63 – 0.81]	
Irregular	2	2	96	4	29 (23)	24 (19)	23 (18)	0.84 [0.82 – 0.97]	
Light blue crest								0.89 [0.84,0.93]	0.58 [0.49,0.72]
No	95	51	97	76	106 (85)	104 (84)	101 (81)	0.93 [0.90 – 0.96]	
Yes	5	49	3	24	18 (15)	20 (16)	23 (19)	0.65 [0.51 – 0.78]	
White opaque substance								0.93 [0.89,0.97]	0.57 [0.40,0.79]
No	100	95	61	100	117 (94)	111 (89)	111 (89)	0.96 [0.94 – 0.98]	
Yes	0	5	39	0	7 (6)	13 (11)	13 (11)	0.64 [0.47 – 0.77]	
Regularity									
Regular	0	5	15	0	4	8	8		
Irregular	0	0	13	0	3	5	5		
Vascular pattern								0.96 [0.93 – 0.98]	0.89 [0.78 – 0.96]
Regular	98	98	3	96	96 (77)	100 (81)	99 (80)	0.97 [0.96 – 0.99]	
Irregular	2	2	97	4	28 (23)	24 (19)	25 (20)	0.91 [0.82 – 0.97]	
Vascular thickness								0.62 [0.56 – 0.68]	0.19 [0.02 – 0.28]
Thin or ultrathin	28	24	34	22	68 (55)	9 (7)	28 (23)	0.32 [0.22 – 0.41]	
Thick (normal)	72	76	66	78	56 (45)	115 (93)	96 (77)	0.74 [0.68 – 0.79]	
Vascular density								0.65 [0.60 – 0.71]	0.24 [0.13 – 0.36]
Low	34	38	32	43	49 (39)	36 (29)	44 (36)	0.49 [0.39 – 0.59]	
High (normal)	66	62	68	57	75 (61)	88 (71)	80 (65)	0.73 [0.67 – 0.78]	
Variable vascular density								0.61 [0.55 – 0.67]	0.21 [0.09 – 0.35]
No (normal)	61	47	0	38	55 (57)	54 (54)	56 (57)	0.66 [0.58 – 0.73]	
Yes	39	53	100	62	41 (43)	46 (46)	43 (43)	0.55 [0.46 – 0.63]	

[1] Endoscopists with previous clinical experience of NBI (>50 NBI gastroscopies).

[20 high grade, 3 low grade]), 50 of which *H. pylori* positive, were recorded to accompany 140 histological samples.

Accuracy and reproducibility of previously described NBI features

The correlation of different NBI features with histology, the reliability measures for all described NBI features, and the presumptive histological results are shown in **Table 2** and **Table 3**.

The identification of different mucosal and vascular patterns was associated with high reproducibility (Pa > 80% with k = 0.71 and k = 0.89, respectively). The identification of LBC or WOS was also associated with substantial reproducibility (Pa > 80% with k = 0.58 and k = 0.57, respectively). Conversely, other vascular features such as thickness or density had only weak to moderate reproducibility (Pa = 0.62 and Pa = 0.65 with k = 0.19 and k = 0.24, respectively).

Variable vascular density was the most accurate parameter for identification of *H. pylori* gastritis, although inter-observer agreement was only fair (Pa = 0.61 and k = 0.21).

Mucosal and vascular patterns derived from the histology results were highly valid for metaplasia and dysplasia (**Table3**). The histological diagnosis proposed by the observers showed a high agreement with histological diagnosis (Pa = 0.82, k = 0.71) but only a weak to moderate agreement for *H. pylori* infection (Pa = 0.61, k = 0.21).

Development of a simplified classification

Using the results from the derivation study, a simplified classification of gastric lesions was established (**Table 4** and **Fig.2**).

The presence of LBC contributed but was not essential to the diagnosis of intestinal metaplasia. Also, WOS contributed to the diagnosis of dysplasia or cancer; however, it could only be considered when an irregular mucosal/vascular pattern was seen.

Validation study

Description of participants and videos

The characteristics of patients and endoscopic procedures included in the validation study are shown in **Table 1**, and were similar to those of the derivation study. Dysplasia in previous biopsies and mucosectomy were important indications for endoscopy (45%). A total of 100 good quality videos (40 normal mucosa, 38 intestinal metaplasia, 22 dysplasia [19 high grade, 3 low grade], and 39 of which had *H. pylori*) were recorded to accompany 119 histological samples.

Accuracy and reproducibility of the new NBI classification

Table5 shows the correlation between NBI patterns and histological findings, inter-observer agreement, and accuracy for the different NBI patterns proposed. WOS was not evaluated because only one cancer lesion presented this feature in the validation study. The identification of the different patterns was associated with substantial reproducibility (Pa = 0.76, k = 0.62). There were no differences in the reproducibility between the experts and the experienced observers. However, the agreement between the group of experienced observers was higher when compared with the non-experienced group (k = 0.75 vs. 0.60). The identification of the LBC was associated with a moderate agreement (Pa = 0.77, k = 0.49); again, however, this agreement was better between the experienced than between the non-experienced observers (k = 0.77 vs. k = 0.40, respectively). The reproducibility of the variable vascular density NBI pattern for *H. pylori* was fair to moderate (Pa = 0.71, k = 0.38) with no differences between the groups.

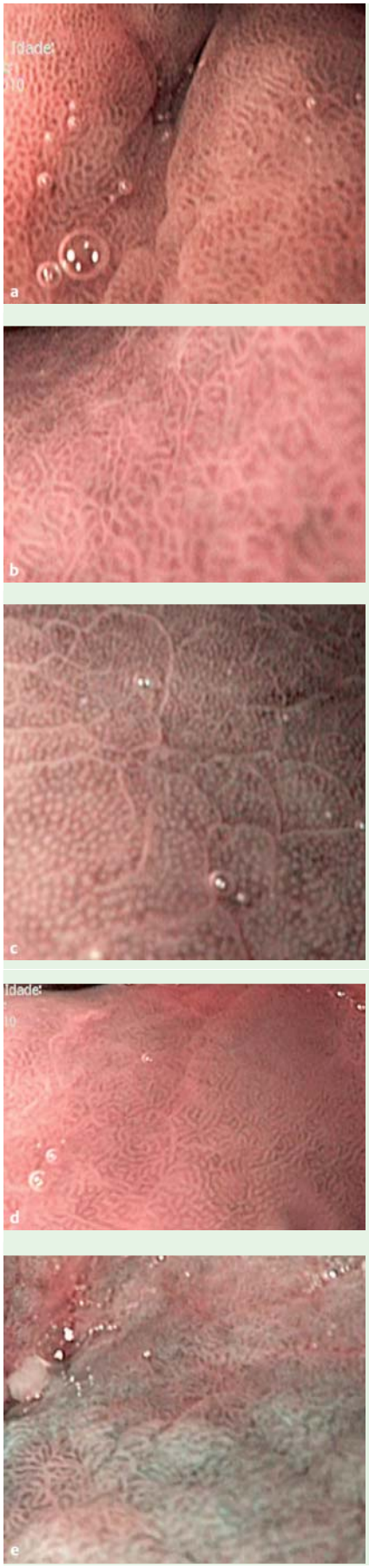
The new NBI patterns derived and proposed were highly accurate for metaplasia and, in particular, for dysplasia (**Table 5**). The accuracy of the patterns (A – C) was higher in the experts and experienced observers compared with the non-experienced (pat-

Table 3 Derivation study: features on narrow band imaging with accuracy estimates for the diagnosis of the several gastric lesions.

Mucosal/vascular pattern	Outcome	Mean sensitivity (range) [95%CI]	Mean specificity (range) [95%CI]	Mean accuracy (range) [95%CI]
Regular, tubulo-villous	Intestinal metaplasia	0.89 (0.85 – 0.94) [0.78 – 1.00]	0.90 (0.88 – 0.95) [0.84 – 0.96]	0.90 (0.87 – 0.94) [0.85 – 0.95]
Irregular	Dysplasia	0.96 (0.92 – 1.00) [0.82 – 1.00]	0.98 (0.96 – 0.99) [0.92 – 1.00]	0.97 (0.97 – 0.98) [0.95 – 1.00]
Light blue crest	Intestinal metaplasia	0.48 (0.42 – 0.55) [0.31 – 0.66]	0.96 (0.95 – 0.97) [0.89 – 0.99]	0.83 (0.81 – 0.85) [0.77 – 0.90]
Variable vascular density	*H. pylori* infection	0.62 (0.45 – 0.69) [0.46 – 0.75]	0.70 (0.58 – 0.78) [0.56 – 0.82]	0.66 (0.52 – 0.73) [0.56 – 0.75]

Table 4 Proposed classification for gastric lesions on narrow band imaging. Regular mucosal and vascular patterns favor the absence of dysplasia, ridge or tubulo-villous being found in areas with intestinal metaplasia. The light blue crest should be considered specific for intestinal metaplasia but its absence does not exclude intestinal metaplasia. A variable vascular density may favor the presence of *H. pylori* infection.

	Proposed classification				
	A	B		Hp+	C
Mucosal pattern	Regular circular	Regular ridge/tubulo-villous	Light blue crest	Regular	Irregular/absent White opaque substance
Vascular pattern	Regular Thin/peripheric (body (b) or thick/central (a) vessels	Regular		Regular with variable vascular density	Irregular
Expected outcome	Normal	Intestinal metaplasia		H. pylori infection	Dysplasia



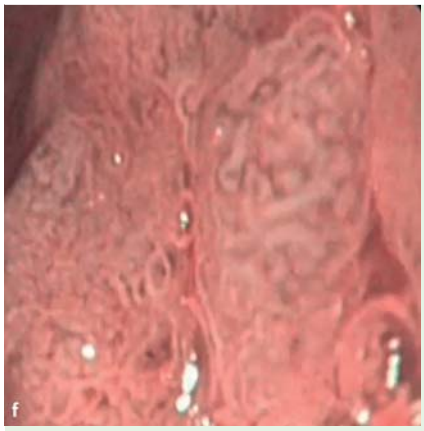


Fig. 2 The simplified classification of gastric lesions using narrow band imaging. **a** Pattern Aa – regular circular/oval mucosa surrounding regular thick vessels in the center of the gland; histology showed normal antrum mucosa; **b** Pattern Aa+– variable vascular density with areas of low (right) and high (top and center) density but with a pattern of a normal antrum; histology showed *H. pylori* gastritis. These areas of low or high density may render the visualization of narrow band imaging (NBI) features difficult, however, they should not be confused with the irregularity seen in dysplasia (f); **c** Pattern Ab – regular circular mucosa that is surrounded by regular vessels, not in the center of the gland as in the antrum; histology showed normal body mucosa. It is important to recognize that normal body and antrum mucosa have a slightly different NBI appearance; **d** Pattern B – regular ridge/tubulo-villous mucosa with regular vessels; histology showed intestinal metaplasia; **e** Pattern B+with light blue crest – ridge mucosa with some blue-whitish slightly raised areas and a variable vascular density; histology showed intestinal metaplasia with *H. pylori* gastritis; **f** Pattern C – irregular mucosa with irregular vessels and a complete architectural loss of the mucosal and vascular pattern; this flat lesion presented high grade dysplasia.

tern A: accuracy 87% vs. 74%; pattern B: 88% vs. 76%; pattern C: 97% vs. 91%) as well as the accuracy of LBC (87% vs. 81%). There were no differences between the groups with regard to *H. pylori* pattern accuracy.

The predictive values for the classification were as follows (**Table 6**). For the diagnosis of intestinal metaplasia using pattern B, a likelihood ratio for a positive test (presence of a certain mucosal pattern) was estimated to be 4.75 and the likelihood ratio of its absence (LR–) was 0.13. The diagnosis of intestinal metaplasia using LBC showed LR+=5.13 and LR–=0.37. Variable vascular density produced predictive values of LR+=2.53 and LR–=0.48. Importantly, pattern C presented LR+=44.33 and LR–=0.16 for dysplasia.

Discussion

To the best of our knowledge this is the first study of reproducibility and validity of HR-NBI endoscopy for the identification of several different gastric lesions that incorporates the entire spectrum of precancerous and intestinal-type cancer lesions. The study provides significant evidence that NBI endoscopy may be a reproducible and accurate method for the diagnosis of gastric pre-neoplastic and cancer lesions. Indeed, some NBI features were very reproducible and were associated consistently with gastric lesions. Furthermore, it appears that a learning curve for the identification of these NBI features should be allowed for, as

Table 5 Validation study: correlation between features on narrow band imaging (NBI) and histology, and reproducibility and diagnosis accuracy of the simplified NBI patterns.

	Overall reproducibility	Mucosal pattern				Variable vascular density
		A	B	C	Light blue crest	
Observed outcome, %						
Normal		76	22	2	11	39
Intestinal metaplasia		9	89	2	68	49
Dysplasia		2	14	84	17	13
H. pylori infection		39	59	2	41	64
All observers [95 %CI]						
Pa	0.76 [0.71 – 0.80]	0.75 [0.67 – 0.81]	0.74 [0.67 – 0.79]	0.81 [0.72 – 0.87]	0.77 [0.73 – 0.81]	0.71 [0.66 – 0.75]
k	0.62 [0.55 – 0.62]				0.49 [0.38 – 0.58]	0.38 [0.29 – 0.48]
Mean sensitivity (range)		0.76 (0.60 – 1.00) [0.63 – 0.89]	0.90 (0.79 – 1.00) [0.79 – 1.00]	0.84 (0.50 – 1.00) [0.70 – 0.99]	0.68 (0.56 – 0.82) [0.53 – 0.84]	0.64 (0.41 – 0.86) [0.49 – 0.80]
Mean specificity (range)		0.94 (0.83 – 1.00) [0.83 – 0.97]	0.81 (0.61 – 0.98) [0.72 – 0.91]	0.98 (0.95 – 1.00) [0.95 – 1.00]	0.87 (0.68 – 0.98) [0.79 – 0.95]	0.75 (0.56 – 0.95) [0.61 – 0.88]
Mean accuracy (range)	0.82 (0.64 – 0.95) [0.75 – 0.90]	0.83 (0.64 – 0.95) [0.75 – 0.90]	0.84 (0.67 – 0.95) [0.77 – 0.91]	0.95 (0.88 – 1.00) [0.90 – 0.99]	0.80 (0.70 – 0.91) [0.73 – 0.88]	0.70 (0.63 – 0.86) [0.59 – 0.80]
Experts[1] [95 %CI]						
Pa	0.84 [0.78 – 0.90]	0.80 [0.69 – 0.88]	0.83 [0.77 – 0.89]	0.88 [0.78 – 0.96]	0.81 [0.75 – 0.86]	0.71 [0.66 – 0.77]
K	0.75 [0.65 – 0.83]				0.60 [0.47 – 0.72]	0.40 [0.28 – 0.53]
Mean sensitivity (range)		0.69 (0.62,0.76) [0.55 – 0.83]	0.92 (0.85 – 1.00) [0.83 – 1.00]	0.90 (0.83 – 0.96) [0.78 – 1.00]	0.72 (0.56 – 0.82) [0.56 – 0.87]	0.71 (0.57 – 0.86) [0.57 – 0.86]
Mean specificity (range)		0.95 (0.91 – 1.00) [0.86 – 0.98]	0.80 (0.79 – 0.82) [0.70 – 0.89]	0.98 (0.95 – 1.00) [0.95 – 1.00]	0.82 (0.68 – 0.89) [0.73 – 0.91]	0.73 (0.64 – 0.85) [0.59 – 0.87]
Mean accuracy (range)	0.82 (0.77 – 0.86) [0.74 – 0.89]	0.82 (0.77 – 0.86) [0.74 – 0.90]	0.84 (0.81 – 0.86) [0.77 – 0.91]	0.96 (0.94 – 0.99) [0.92 – 1.00]	0.78 (0.73 – 0.94) [0.70 – 0.86]	0.72 (0.63 – 0.86) [0.62 – 0.82]
Experienced observers[2] [95 %CI]						
Pa	0.84 [0.78 – 0.89]	0.85 [0.77 – 0.90]	0.78 [0.69 – 0.86]	0.90 [0.81 – 0.97]	0.91 [0.86 – 0.95]	0.77 [0.71 – 0.83]
K	0.75 [0.65 – 0.83]				0.77 [0.62 – 0.88]	0.46 [0.32 – 0.60]
Mean sensitivity (range)		0.91 (0.79 – 1.00) [0.83 – 1.00]	0.89 (0.82 – 0.94) [0.79 – 1.00]	0.94 (0.88 – 1.00) [0.85 – 1.00]	0.67 (0.59 – 0.79) [0.51 – 0.83]	0.58 (0.41 – 0.68) [0.42 – 0.74]
Mean specificity (range)		0.95 (0.91 – 1.00) [0.86 – 0.98]	0.93 (0.83 – 0.98) [0.87 – 0.99]	0.99 (0.97 – 1.00) [0.96 – 1.00]	0.98 (0.97 – 0.98) [0.95 – 1.00]	0.81 (0.64 – 0.95) [0.69 – 0.93]
Mean accuracy (range)	0.91 (0.86 – 0.95) [0.86 – 0.97]	0.91 (0.86 – 0.95) [0.86 – 0.97]	0.92 (0.87 – 0.95) [0.86 – 0.97]	0.98 (0.95 – 1.00) [0.95 – 1.00]	0.87 (0.85 – 0.91) [0.81 – 0.94]	0.70 (0.63 – 0.80) [0.59 – 0.80]
Non-experienced observers[3] [95 %CI]						
Pa	0.75 [0.68 – 0.82]	0.76 [0.65 – 0.84]	0.76 [0.68 – 0.83]	0.70 [0.56 – 0.82]	0.73 [0.66 – 0.77]	0.73 [0.67 – 0.79]
K	0.60 [0.48 – 0.71]				0.40 [0.26 – 0.53]	0.44 [0.31 – 0.57]
Mean sensitivity (range)		0.67 (0.60 – 0.76) [0.53 – 0.82]	0.87 (0.79 – 0.91) [0.76 – 0.98]	0.68 (0.50 – 0.83) [0.49 – 0.87]	0.67 (0.62 – 0.71) [0.51 – 0.83]	0.64 (0.49 – 0.76) [0.48 – 0.79]
Mean specificity (range)		0.92 (0.83 – 0.97) [0.85 – 0.99]	0.71 (0.61 – 0.80) [0.60 – 0.82]	0.98 (0.96 – 1.00) [0.95 – 1.00]	0.80 (0.74 – 0.92) [0.71 – 0.90]	0.70 (0.56 – 0.77) [0.56 – 0.84]
Mean accuracy (range)	0.74 (0.64 – 0.83) [0.66 – 0.83]	0.74 (0.64 – 0.83) [0.66 – 0.83]	0.76 (0.67 – 0.84) [0.68 – 0.85]	0.91 (0.88 – 0.94) [0.85 – 0.96]	0.76 (0.70 – 0.84) [0.67 – 0.84]	0.67 (0.66 – 0.72) [0.57 – 0.78]

[1] Three international experts with known interest in NBI.
[2] The three experienced endoscopist (End1, End2, and End3) who participated in the derivation study
[3] Three different gastroenterologists with special interest in chromoendoscopy but with diverse NBI experience (<50 NBI gastroscopies).

Table 6 Estimates of predictive values.

Outcome	Feature	LR+	Positive predictive value, %				LR–	Negative predictive value, %			
			1%	10%	20%	50%		1%	10%	20%	50%
Intestinal metaplasia											
	B pattern	4.75	5	34	54	83	0.13	0.10	1	3	11
	Light blue crest	5.13	5	36	56	84	0.37	0.40	4	8	27
Dysplasia											
	C pattern	44.33	31	83	92	98	0.16	0.20	2	4	14

LR, likelihood ratio

expertise is associated with a more precise identification of the lesions and a more accurate diagnosis.

The main limitations to the study were the fact that NBI features were not compared with HR-WLE and that some gastric lesions that can present dysplasia, such as erosions or ulcers, were not included. Also not included were some gastric pathologies that are associated with increased cancer risk, such as autoimmune gastropathy (pernicious anemia) or Ménétrier disease. Therefore, the results should be regarded as applicable to patients with precancerous conditions and intestinal Lauren-type gastric adenocarcinoma. In addition, as low grade dysplasia was observed in only six lesions it cannot be accurately stated that the classification will be applicable equally to low grade dysplasia and high grade dysplasia/intramucosal adenocarcinoma. Also, diffuse-type adenocarcinomas were not included in the current study.

Other studies have provided interesting results on the role of NBI for the detection of gastric pre-neoplastic and cancer lesions [11–24]. However, there are several aspects of the previous studies that must be borne in mind. The definitions of the NBI features were different between the studies, only one study evaluated the reproducibility of some NBI features, and no single study included the whole spectrum of gastric lesions in the same classification or evaluation [25]. Moreover, almost all of the data come from Japan, and therefore applicability to Western countries is uncertain. Another consideration is that almost all of the previous studies used NBI with high magnification (up to ×80), which is not practical in clinical routine as these endoscopes are not available in most centers, at least not in Western countries.

To our knowledge, only three other studies have attempted to identify *H. pylori* gastritis. Alaboudy et al. [23] was the only study that used NBI without magnification; however, the NBI patterns in this study were complex and no reproducibility analysis of these complex patterns was undertaken. Bansal et al. [11] associated irregularity of mucosal and vascular patterns and a low vascular density to *H. pylori* gastritis. However, they did not define irregularity, nor was any reproducibility analysis undertaken, and a low number of patients was included. Tahara et al. [19] associated *H. pylori* gastritis to different patterns with enlarged pits and increased density of irregular vessels. However, again, no reproducibility analysis was done and in neither of these studies was dysplasia considered. This is important because, in our opinion, the "irregularity" described by those studies is clearly different from the irregularity that is present in cancer lesions. To overcome this problem in the current study, irregularity and the different patterns described in previous studies was defined as "variable vascular density," which did indeed show a positive association with *H. pylori* gastritis; however, the reproducibility of this feature on NBI was relatively low and independent of expertise. The results from all of the studies suggest that, even though NBI may be superior to WLE for the identification of *H. pylori* gastritis, NBI (at least without magnification) does not replace other diagnostic tests (e.g. histology) that are clearly more sensitive, specific, and reproducible.

In the case of intestinal metaplasia identification, however, the existing evidence suggests that NBI may be an important tool. Indeed, the two studies by Bansal and Tahara associated a tubulovillous mucosal pattern to intestinal metaplasia with great accuracy [11, 19]. These results were confirmed in the present study, with 92% accuracy of this mucosal pattern for the diagnosis of metaplasia by experienced observers. Uedo et al. [21] suggested that the finding of LBC with NBI is also very accurate for intestinal metaplasia; reproducibility of this finding was not evaluated in the study. In the current study, however, LBC was not very sensitive for metaplasia (68% global sensitivity), though it was specific (87% global specificity). Nevertheless, at least when using a low magnification and the Olympus EXERA system (Uedo used high magnification and the LUCERA system), it appears that a tubulovillous mucosal pattern is more consistently associated and in a more reproducible manner with metaplasia.

Evaluation of dysplasia/cancer using NBI has been performed in several studies. Initial studies have also attempted to establish NBI patterns that could help to predict the degree of tumor differentiation [13,18,20]. Despite some positive results, the authors concluded that NBI was not able to replace histology for tumor differentiation [18]. In these studies, however, the authors did not evaluate which NBI features could help to differentiate between benign and dysplastic lesions. Some authors suggest that "adenoma" may have an NBI pattern resembling pattern B in the current study [20,22], but the precise histological diagnosis of the lesions was not provided in previous studies and it is likely that they presented foci of low grade dysplasia in the context of extensive intestinal metaplasia. In contrast, Kaise et al. [16] evaluated NBI criteria for cancer diagnosis in gastric depressed lesions. They concluded that irregular vascular and mucosal patterns were very specific for cancer, although sensitivity was low and reproducibility only moderate. These relatively modest results may be because cancer lesions were compared only with a particular benign lesion – gastric erosions. Indeed, the same group of authors using the same criteria for dysplasia but evaluating different suspicious lesions found that the sensitivity and specificity of magnification endoscopy NBI for the diagnosis of dysplasia were > 90% [29]. Ezoe et al. [14] obtained similar results using similar NBI criteria. In the current study, the accuracy of irregular mucosal and vascular patterns, considered as a complete architecture distortion, was evaluated for the diagnosis of gastric dysplasia in the context of all benign lesions and using only low

magnification. The results were very impressive, showing not only that these NBI criteria are very accurate for the diagnosis of dysplasia, similar to the study of Kato et al. [29], but also that they allow dysplasia diagnosis in a very reproducible manner. Taking all of the evidence together, it can be suggested that this pattern irregularity with NBI appears to be a good method for the diagnosis of gastric dysplasia, at least for high grade dysplasia.

What is the clinical utility of all these aspects? The current study is not a comparative study of NBI with WLE, it is not possible to state whether or not NBI is better than WLE for the diagnosis of gastric lesions. However, comparing the current results with those from other studies that used HR-WLE [30–32] NBI appears to be clearly superior to WLE for the diagnosis of these types of gastric lesions. More importantly, Kaise et al. [16], Ezoe et al. [14], and Kato et al. [29] compared WLE with NBI for the diagnosis of cancer and concluded that the accuracy of NBI is significantly superior to WLE. Recently, Cappelle et al. [12] compared the yield of NBI to WLE in the surveillance of patients with a previous history of intestinal metaplasia or dysplasia. They used the same NBI system as in the current study and similar definitions; however, *H. pylori* gastritis was not considered and no reproducibility analysis was done. Capelle et al. showed that NBI was better than routine WLE for the diagnosis of intestinal metaplasia and dysplasia. Taking all of these data together, we can say that NBI may help to select suspicious areas for biopsy and probably replace the random biopsy method with a biopsy strategy directed to the suspicious areas of metaplasia and/or dysplasia. Moreover, NBI can also help to delineate gastric lesions for endoscopic gastric resection. Indeed, Kadowaki et al. [15], using similar NBI criteria for dysplasia, have shown that NBI is better than WLE for early cancer demarcation recognition.

Another aspect that is relevant to the current study is the fact that endoscopists with more NBI experience and expertise recognize NBI patterns with more agreement and with more diagnostic accuracy. This is important as it reflects a learning curve for this new technology and suggests that even highly experienced endoscopists should undergo training before using NBI in clinical routine. Moreover, data are presented as range of expected values for accuracy. These results may therefore help endoscopists to judge the accuracy of their diagnosis when NBI is used for the assessment of gastric lesions in clinical practice.

Using likelihood ratios, it was possible to estimate the predictive values of this classification in different scenarios (**Table 6**). For reference centers in countries with a high prevalence of precancerous and cancerous lesions, as in Portugal and Eastern European countries, this classification will able to confirm/predict the presence of dysplasia (post-test probability or positive predictive values of 83%–98%) and to exclude both intestinal metaplasia and dysplasia within centers of low prevalence countries (negative predictive value lower than 1%). Further studies of a per-patient assessment of utility in such specific settings, namely by comparing NBI with WLE or other technologies are needed.

In conclusion, HR-NBI endoscopy is an efficacious technique for the characterization of gastric intestinal metaplasia and, in particular, dysplasia. Irregularity of vascular/mucosal pattern is identified in a reproducible manner and it is consistently associated with gastric dysplasia. HR-NBI endoscopy may be an important tool for the early diagnosis of gastric pre-neoplastic and neoplastic lesions and for therapeutic procedures.

Competing interests: None

Institutions

[1] Department of Gastroenterology, Portuguese Oncology Institute of Porto, Porto, Portugal
[2] Department of Physiology, Cardiovascular Research and Development Unit, Porto Faculty of Medicine, Porto University, Porto, Portugal
[3] CINTESIS/Biostatistics and Medical Informatics, Faculty of Medicine, Porto University, Porto, Portugal
[4] Department of Gastroenterology, Hospital de Braga, Braga, Portugal
[5] Department of Gastroenterology, Centro Hospitalar do Porto, Porto, Portugal
[6] Surgical Sciences Research Domain, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal
[7] Department of Gastroenterology, Hospital de São João, Porto, Portugal
[8] Department of Gastroenterology, Portuguese Oncology Institute of Coimbra, Coimbra, Portugal
[9] Department of Pathology, Portuguese Oncology Institute of Porto, Porto, Portugal
[10] Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherland
[11] Division of Gastroenterology and Hepatology, Veterans Affairs Medical Center, Kansas City, Missouri, USA
[12] Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan
[13] Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

Acknowledgments

This study was supported by a grant for medical investigation from the Portuguese Digestive Endoscopy Society (SPED 2009 Investigation Grant).

This study was in part presented as an oral communication at the 18th United European Gastroenterology Week, 23–27 October 2010; Barcelona, Spain.

References

1 *Parkin DM, Bray F, Ferlay J* et al. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001; 94: 153–156
2 *Hundahl SA, Menck HR, Mansour EG* et al. The National Cancer Data Base report on gastric carcinoma. Cancer 1997; 80: 2333–2341
3 *Correa P.* Human gastric carcinogenesis: a multistep and multifactorial process – First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992; 52: 6735–6740
4 *deVries AC, van Grieken NC, Looman CW* et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. Gastroenterology 2008; 134: 945–952
5 *Stemmermann GN, Fenoglio-Preiser C.* Gastric carcinoma distal to the cardia: a review of the epidemiological pathology of the precusors to a preventable cancer. Pathology 2002; 34: 494–503
6 *Lin BR, Shun CT, Wang TH* et al. Endoscopic diagnosis of intestinal metaplasia of stomach – accuracy judged by histology. Hepatogastroenterology 1999; 46: 162–166
7 *Redeen S, Petersson F, Jonsson KA* et al. Relationship of gastroscopic features to histological findings in gastritis and Helicobacter pylori infection in a general population sample. Endoscopy 2003; 35: 946–950
8 *Areia M, Amaro P, Dinis-Ribeiro M* et al. Estimation of the extent of gastric intestinal metaplasia by methylene blue chromoendoscopy. Eur J Gastroenterol Hepatol 2008; 20: 939–940
9 *Areia M, Amaro P, Dinis-Ribeiro M* et al. External validation of a classification for methylene blue magnification chromoendoscopy in premalignant gastric lesions. Gastrointest Endosc 2008; 67: 1011–1018
10 *Dinis-Ribeiro M, da Costa-Pereira A, Lopes C* et al. Magnification chromoendoscopy for the diagnosis of gastric intestinal metaplasia and dysplasia. Gastrointest Endosc 2003; 57: 498–504
11 *Bansal A, Ulusarac O, Mathur S* et al. Correlation between narrow band imaging and nonneoplastic gastric pathology: a pilot feasibility trial. Gastrointest Endosc 2008; 67: 210–216
12 *Capelle LG, Haringsma J, de Vries AC* et al. Narrow band imaging for the detection of gastric intestinal metaplasia and dysplasia during surveillance endoscopy. Dig Dis Sci 2010; 55: 3442–3448
13 *Endo T, Nosho K, Arimura Y* et al. Study of the tumor vessels in depressed-type early gastric cancers using narrow band imaging magnifying endoscopy and cDNA array analysis. Digestive Endoscopy 2005; 17: 210–217

14 *Ezoe Y*, *Muto M*, *Horimatsu T* et al. Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study. Gastrointest Endosc 2010; 71: 477 – 484
15 *Kadowaki S*, *Tanaka K*, *Toyoda H* et al. Ease of early gastric cancer demarcation recognition: a comparison of four magnifying endoscopy methods. J Gastroenterol Hepatol 2009; 24: 1625 – 1630
16 *Kaise M*, *Kato M*, *Urashima M* et al. Magnifying endoscopy combined with narrow-band imaging for differential diagnosis of superficial depressed gastric lesions. Endoscopy 2009; 41: 310 – 315
17 *Kato M*, *Kaise M*, *Yonezawa J* et al. Trimodal imaging endoscopy may improve diagnostic accuracy of early gastric neoplasia: a feasibility study. Gastrointest Endosc 2009; 70: 899 – 906
18 *Nakayoshi T*, *Tajiri H*, *Matsuda K* et al. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). Endoscopy 2004; 36: 1080 – 1084
19 *Tahara T*, *Shibata T*, *Nakamura M* et al. Gastric mucosal pattern by using magnifying narrow-band imaging endoscopy clearly distinguishes histological and serological severity of chronic gastritis. Gastrointest Endosc 2009; 70: 246 – 253
20 *Tamai N*, *Kaise M*, *Nakayoshi T* et al. Clinical and endoscopic characterization of depressed gastric adenoma. Endoscopy 2006; 38: 391 – 394
21 *Uedo N*, *Ishihara R*, *Iishi H* et al. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. Endoscopy 2006; 38: 819 – 824
22 *Yao K*, *Iwashita A*, *Tanabe H* et al. White opaque substance within superficial elevated gastric neoplasia as visualized by magnification endoscopy with narrow-band imaging: a new optical sign for differentiating between adenoma and carcinoma. Gastrointest Endosc 2008; 68: 574 – 580
23 *Alaboudy AA*, *Elbahrawy A*, *Matsumoto S* et al. Conventional narrow-band imaging has good correlation with histopathological severity of Helicobacter pylori gastritis. Dig Dis Sci 2011; 56: 1127 – 1130
24 *Okubo M*, *Tahara T*, *Shibata T* et al. Changes in gastric mucosal patterns seen by magnifying NBI during H. pylori eradication. . J Gastroenterol 2011; 46: 175 – 182
25 *Curvers WL*, *van den Broek FJ*, *Reitsma JB* et al. Systematic review of narrow-band imaging for the detection and differentiation of abnormalities in the esophagus and stomach (with video). Gastrointest Endosc 2009; 69: 307 – 317
26 *Dinis-Ribeiro M*, *Pimentel-Nunes P*, *Afonso M* et al. A European case series of endoscopic submucosal dissection for gastric superficial lesions. Gastrointest Endosc 2009; 69: 350 – 355
27 *Dixon MF*, *Genta RM*, *Yardley JH* et al. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996; 20: 1161 – 1181
28 *Dixon MF*. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 2002; 51: 130 – 131
29 *Kato M*, *Kaise M*, *Yonezawa J* et al. Magnifying endoscopy with narrow-band imaging achieves superior accuracy in the differential diagnosis of superficial gastric lesions identified with white-light endoscopy: a prospective study. Gastrointest Endosc 2010; 72: 523 – 529
30 *Eshmuratov A*, *Nah JC*, *Kim N* et al. The correlation of endoscopic and histological diagnosis of gastric atrophy. Dig Dis Sci 2010; 55: 1364 – 1375
31 *Gonen C*, *Simsek I*, *Sarioglu S* et al. Comparison of high resolution magnifying endoscopy and standard videoendoscopy for the diagnosis of Helicobacter pylori gastritis in routine clinical practice: a prospective study. Helicobacter 2009; 14: 12 – 21
32 *Kato M*, *Kaise M*, *Yonezawa J* et al. Autofluorescence endoscopy versus conventional white light endoscopy for the detection of superficial gastric neoplasia: a prospective comparative study. Endoscopy 2007; 39: 937 – 941

Fig.e1 is available online:

online content viewable at:
www.thieme-connect.de/ejournals/abstract/endoscopy/
doi/10.1055/s-0031-1291537

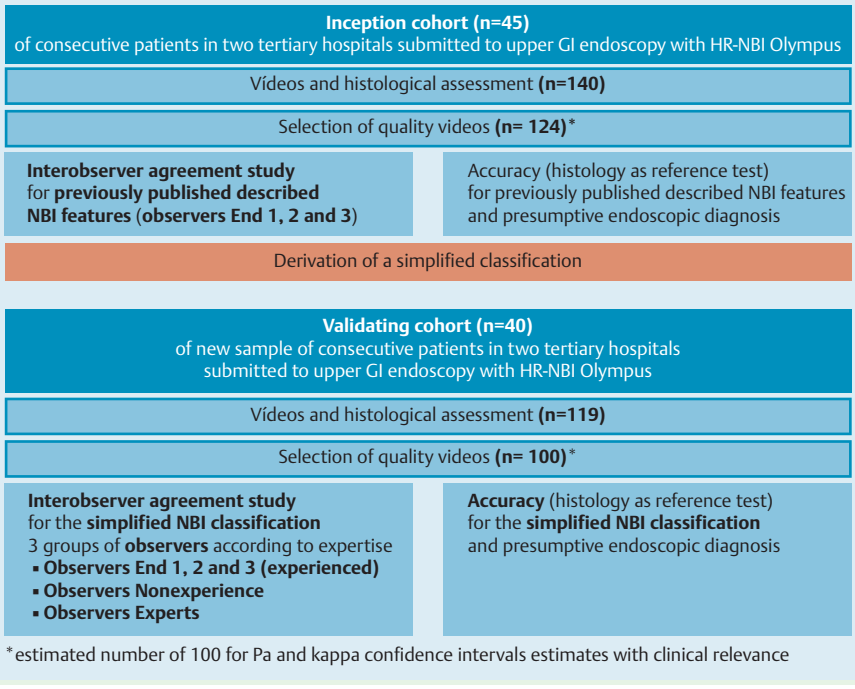


Fig. e1 Two studies were planned: 1) a consecutive sample of 45 patients (yielding an estimated sample of 100 videos), observed across two tertiary hospitals between September and December 2009, constituted the "derivation cohort," which provided data for a reliability study of previously described mucosal and vascular features using high resolution narrow band imaging (HR-NBI) in gastric mucosa [11 – 24]. These features were used to develop a simplified NBI classification, which also considered validity measures (using histology as the reference test); 2) a "validation cohort" of 40 new patients (and a new estimated sample of 100 videos) was assessed between February and April 2010; endoscopic observations were used to validate the new NBI classification and assess the reliability of the classification within groups of endoscopists with diverse experience.